## REMARKS

Applicant respectfully requests reconsideration. Claims 19-35, 37-48, 50-66, 68-79 and 81-112 were previously pending in this application. No claims are amended herein. As a result, claims 19-35, 37-48, 50-66, 68-79 and 81-112 are still pending in the present application, with claims 19, 37, 50, 68, 81, 90, 97 and 106 being independent claims. Claims 19-23, 25-30, 32, 33, 35, 37, 39-44, 46, 48, 50-54, 56-61, 63, 64, 66, 68, 70-75, 77, 79, 81-84, 86, 87, 89-92, 94, 96-100, 102, 103, 105-108, 110 and 112 read on the elected species under examination. No new matter has been added.

### Title of the Invention

The Title of the instant application was objected to as not being descriptive. To address this objection, Applicant has amended the title of the invention so as to clearly indicate the invention to which the claims are directed. Applicant believes that this amendment introduces no new matter. Entry of the amended title is respectfully requested.

### Abstract of the Invention

The Examiner objected to the Abstract of the Invention because the abstract did not reflect or clearly describe the instantly claimed invention. In response, Applicant has amended the Abstract so as to reflect and clearly describe the claimed invention. Applicant believes that this amendment introduces no new matter. Entry of the amended Abstract is respectfully requested.

### Rejections under 35 U.S.C. 112

#### *Written Description Requirement*

Claims 19-23, 25, 30, 32, 33, 35, 37, 39, 44, 46, 48, 50-54, 56, 61, 63, 64, 66, 68, 70, 75, 77, 79, 81-84, 86, 87, 89, 90-92, 94, 96-100, 102, 105-108, 110 and 112 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The Examiner, referring to claim 19 as an example, particularly points out that the subject claims under rejection "only provide that the immunostimulatory nucleic acid has 2 nucleotides (C and G)...the specification does not teach an immunostimulatory nucleic acid molecule *having only 2 nucleic acids*" (Office Action, page 4; emphasis added). On this basis, the Examiner argues that the "[instant application] do not set forth a structure for the claimed immunostimulatory nucleic acid molecule."

Applicant respectfully disagrees for the following reasons.

Applicant respectfully contends that the Examiner has mischaracterized the claim language at issue. Claim 19 recites "A method for treating a mycobacterial infection in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule *comprising* an unmethylated CpG dinucleotide, in an amount effective to treat or ameliorate an infection with a Mycobacterium bacterium, thereby treating the infection in the subject" (emphasis added). Thus, the claim is readable upon methods using immunostimulatory nucleic acid sequences that are characterized by the presence of a CpG motif, rather than limited to CpG dinucleotides.

The Examiner stated, on page 5 of the Office Action, the following:

> Moreover, because the claims encompass a genus of an immunostimulatory nucleic acid molecule, and adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction of drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However...nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

With regard to the issue of possession, Applicant wishes to point out that the immunostimulatory nucleic acids of the claimed invention were not derived merely on a theoretical basis. Rather, as stated in the specification as filed, over 300 ODNs of various lengths and sequences, with or without a CpG, either methylated or unmethylated, were synthesized and tested for their immunostimulatory activity. Based on the experimental results, it was determined that the unmethylated CpG motif conferred the observed immunostimulatory effect. Based on this, Applicant respectfully argues that such "distinguishing, identifying characteristics" based on "at

least a representative number of species" are in fact disclosed in the application. Indeed, "an unmethylated CpG dinucleotide" recited in the instant claims under rejection does represent distinguishing, identifying characteristics" of the claimed genus. The apparent simplicity of the distinguishing, identifying characteristics, e.g., an unmethylated CpG, should not be construed as a lack of an adequate description.

On page 9 of the Office Action, the Examiner contends that "[i]t is noted that Applicants have claimed a large genus of CpG immunostimulatory nucleic acid molecules with only the C and G being defined in the immunostimulatory nucleic acid molecule. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice." Throughout the specification, numerous species of nucleic acid molecules of various lengths and sequences and their immunostimulatory effects are disclosed. Therefore, contrary to the Examiner's assertion ("...absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of compositions, the skilled artisan could not immediately recognize or distinguish..."), the instant application sufficiently describes the scope of a genus of the claimed invention, as well as numerous species of the genus. As should be clear to those skilled in the art, based on the disclosure of the instant invention, the immunostimulatory nucleic acids have in common (e.g., distinguishing, identifying characteristics) an unmethylated CpG dinucleotide. Thus, the present specification adequately provides descriptions in compliance with the written description requirement under 35 U.S.C. § 112, first paragraph. Accordingly, it is respectfully requested that these rejections be reconsidered and withdrawn.

***Enablement Requirement***

Claims 19-23, 25-30, 32, 33, 35, 37, 39-44, 46, 48, 50-54, 56-61, 63, 64, 66, 68, 70-75, 77, 79, 81-84, 86, 87, 89-92, 94, 96-100, 102, 103, 105-108, 110 and 112 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully disagrees.

The Examiner acknowledged that "the specification discloses a list of immunostimulatory nucleic acids that could be used in the claimed invention" but argues that "they comprise 8 or more

nucleotides...not 6 nucleotides as set forth in claim 19" (Office Action, page 12). However, Applicant wishes to point out that claim 19 does *not* recite "6 nucleotides" as asserted by the Examiner. As previously presented, claim 19 recites:

A method for treating a mycobacterial infection in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide, in an amount effective to treat or ameliorate an infection with a Mycobacterium bacterium, thereby treating the infection in the subject.

Accordingly, the argument presented by the Examiner seems misplaced.

The Examiner further argued that "[t]he specification does not teach any of the methods as set forth in the instant claims for treating, preventing or ameliorating mycobacterium infections in a subject" (Office Action page 12). The Examiner alleged that the "data do not indicate enablement for the claimed invention" and further pointed out that "none of the claims recite the administration of an antigen from a mycobacterium" (Office Action, pages 12-13).

A mycobacterium infection is caused by a pathogen, mycobacterium, entering and infecting a host and resulting in pathogenic conditions such as tuberculosis. It has been known in the art that a host immune system responds to such pathogens by activating a number of immune responses, including the innate immunity and the adaptive immunity. The former is generally an early (or already existing) response and involves primarily the action of Natural Killer (NK) cells, which can provide a defense against pathogens. In addition, as part of the adaptive immunity, B cells perform the role of immune surveillence, thereby promoting antibody production. Indeed, the instant application provides, *inter alia*, a number of working examples demonstrating that CpG-containing immunostimulatory oligonucleotides can activate lymphocytes, such as NK cells and B cells. Thus, contrary to the Examiner's position, the instant application presents data to support that administration of an immunostimulatory CpG oligonucleotide can stimulate a subject's immune response in such a way that would facilitate the body's defense against an infection. The skilled artisan would therefore reasonably conclude that such an agent that can enhance or stimulate the immune response would have a beneficial effect for a subject infected with mycobacterium to promote an immunological defense against the pathogen.

It was also known that patients with suppressed immune function (e.g., immune deficiency) were more susceptible to a mycobacterium infection (see, for example, the abstract of Fertel D. & Pitchenik AE., Seminars in Respiratory Infections, 1989 Sep;4(3):198-205, submitted herewith as Exhibit A, that reports that "TB occurs early ... in the course of progressive HIV-induced immunosuppression") indicating that a normal immune system can provide at least some degree of protection against the pathogenesis caused by a mycobacterium infection. Thus, based on the teaching of the instant application, in view of the state of the art at the time of filing of the application, one of ordinary skill would reasonably believe that the immunostimulatory nucleic acids of the instant invention would be useful for treating a subject infected with mycobacterium.

In view of the foregoing, Applicant submits that the instant claims are enabled. Accordingly, Applicant respectfully requests that the rejections made under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

## CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: December 5, 2007

Respectfully submitted,

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# *Seminars in* Respiratory Infections

EDITED BY
GEORGE A. SAROSI, MD

## Update on Tuberculo

*Guest Editor*
Asim K. Dutt, MD

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.

# Tuberculosis in Acquired Immune Deficiency Syndrome

Debra Fertel and Arthur E. Pitchenik

**The acquired immune deficiency syndrome (AIDS) epidemic has resulted in a rising incidence of tuberculosis (TB) in the United States, especially in inner cities where AIDS is prevalent and among human immunodeficiency virus (HIV) infected subpopulations with a relatively high background prevalence of tuberculous infection (ie, intravenous drug abusers, Haitians, blacks). Because *M tuberculosis* is a relatively virulent organism among the AIDS related infections, TB occurs early (often as a sentinel disease) in the course of progressive HIV-induced immunosuppression. In this setting, TB commonly presents in a disseminated, extrapulmonary, or "unusual" form, and when pulmonary TB occurs, the chest radiographic picture is often atypical. Further, the tuberculin test is falsely negative in more than 50% of cases. A high index of suspicion and an aggressive diagnostic approach is required to avoid missing HIV-related tuberculous disease, which is communicable to the general population and is readily treatable with conventional anti-TB drugs. In order to control the rising incidence of AIDS-related TB, tuberculin skin testing must be performed early for all patients who are either HIV infected or are in high risk groups for HIV infection (while they can still react to tuberculin), and isoniazid prophylaxis carried out for those who are tuberculous infected.**


THE incidence of tuberculosis (TB) in the United States has increased recently, reflecting new demographic trends that have paralleled the onset of the acquired immune deficiency syndrome (AIDS) epidemic.[1-6] From the time national reporting of TB was instituted 3 decades ago, the average number of new TB cases reported to the Centers for Disease Control consistently declined an average of 5% per year, a decline that was attributed to the development and widespread use of effective anti-TB chemotherapy. In the early 1980s, the number of new TB cases reported continued at this rate of decline, representing approximately 1,700 fewer cases per year. By the mid 1980s the trend began to change. In 1985, the number of new TB cases declined by .2% or 54 cases, and in 1986, for the first time since national reporting of TB was instituted, the number of new TB cases rose by 2.6%, an increase of 567 new cases over the previous year. In 1987 and 1988 the incidence of TB remained at a relatively high level. There is compelling evidence that this trend is related to the AIDS epidemic.

## EPIDEMIOLOGY

In high risk areas for AIDS, ie, New York, New Jersey, California, Texas, and South Florida, the number of new TB cases reported to the Centers for Disease Control has been disproportionately high.[1] In New York City, which has the largest number of AIDS cases thus far, the number of new reported cases of TB between 1984 and 1986 rose by 36%, with the greatest increases occurring in those areas of the city with a high incidence of AIDS.[7,8] Further, in New York and other cities, the groups with the greatest increases in TB incidence were the same as those with large numbers of AIDS cases (ie, black and hispanic males aged 25 to 44 years).[6-11]

The correlation between the rising number of TB cases and the AIDS epidemic is supported by additional public health data. There is a much higher incidence of TB among AIDS patients (ranging from 2% to 30%) then in the general population, even after adjustment for age, race, and sex.[6-13] Matching of AIDS and TB registries in 25 states and 4 localities indicated that 680 of 14,902 AIDS patients (4.6%) had TB. This is almost 500 times the 1986 national incidence of TB (.0094%) within the general population.[6] Although the prevalence of TB is high among all AIDS populations compared with the general population, racial and ethnic minorities (ie, black and hispanic males), Haitian immigrants, and intravenous (IV) drug abusers with AIDS have a particularly high prevalence of TB.[9-11] The proportion of AIDS/TB cases who were black or hispanic ranged from 32% in San Francisco to 81% in New York City to 90% in Florida to 100% in Newark.[6] In the state of Florida, the prevalence of TB was 30.2% among 182 Haitians with AIDS, 13.5% among 148 IV drug abusers with

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AIDS, but only 3.6% among 632 homosexual and bisexual men with AIDS.[9] The difference reflects background prevalence of tuberculous infection in these groups. TB is endemic in Haiti, and 80% to 90% of Haitian immigrants entering Florida are reported to have positive tuberculin skin tests.[14] Likewise, 22% to 24% of the drug addicts treated in New York and New Jersey methadone programs have positive tuberculin skin test reactions.[15] It is therefore not surprising that when these subgroups with a high background prevalence of tuberculous infection acquire human immunodeficiency virus (HIV) infection and subsequent immunosuppression, they are likely to develop clinically active TB.

Perhaps the best evidence linking TB and HIV infection is shown by prospective studies of HIV-seropositive and HIV-seronegative IV drug abusers. In one study, conducted in New York City,[16] a cohort of 519 IV drug abusers were followed from 1984 through 1986. Of the 279 persons who were HIV positive or with clinical AIDS, 12 developed TB, while none of the 249 HIV-negative persons developed TB ($P = .0005$). In another, more recent study, conducted in the Bronx, New York,[17] tuberculin skin testing and testing for the HIV antibody were performed on 520 IV drug abusers who were then followed from 3 to 30 months. Forty nine (23%) of 217 HIV-seropositive subjects and 62 (20%) of 303 HIV-seronegative subjects had a positive (Mantoux) tuberculin skin test before entry into the study ($P$ not significant). During the study period, the rates of conversion from a negative to a positive tuberculin test were 15 (11%) of 131 seropositive subjects and 26 (13%) of 202 seronegative subjects ($P$ not significant). Active TB developed in eight of the HIV-seropositive subjects (4%) and in none of the seronegative subjects during the study period ($P < .002$). The authors concluded that the prevalence and incidence of tuberculous infection (detectable by a tuberculin skin test) were similar for both HIV-seropositive and HIV-seronegative groups, yet the risk of active TB was increased only for the seropositive patients, presumably as they became increasingly immunosuppressed. This underscores the importance of performing tuberculin skin tests early in subjects who are HIV seropositive or in high risk groups for AIDS (while they can still react to tuberculin) and promptly instituting anti-TB chemoprophylaxis among those who are tuberculous infected.

When compared to other HIV-related infections, eg, *Pneumocystis carinii* and *Mycobacterium avium-intracellulare* (MAI), *Mycobacterium tuberculosis* is a relatively virulent organism and is therefore usually seen early during the course of progressive T-cell immunosuppression. Multiple studies have confirmed the fact that when HIV-infected patients develop TB, it is often the first AIDS-related infection they get and may precede other AIDS-related infections by months to years.[7-13,18-25] TB may coexist with other opportunistic infections or may be diagnosed following them, but this occurs less often. Of 109 patients in Florida with TB and AIDS, TB preceded the diagnosis of AIDS by more than 1 month in 57% of cases, occurred within 1 month of the diagnosis of AIDS in 28% of cases, and followed the diagnosis of AIDS by more than 1 month in only 16% of cases. The median interval from the time of diagnosis of TB until the time of diagnosis of AIDS (nontuberculous AIDS related diseases) was approximately 3 months.[9] Among 422 consecutive TB patients screened for HIV infection by the Dade County Florida Health Department, 99 (23.5%) were seropositive. Of the 99 HIV-seropositive TB patients, only 13 (13%) met non-TB criteria for AIDS at the time of TB diagnosis.[6,19,23] This indicates that in high risk areas for AIDS, HIV infection may be prevalent among patients with TB, TB often occurs early among the AIDS-related infections, and overt AIDS among HIV-infected TB patients may only be "the tip of the iceberg."

## CLINICAL FEATURES

Patients with HIV-related TB present with fever, weight loss, malaise, cough, and/or night sweats. These symptoms are nonspecific, occur commonly with other AIDS-related diseases, and are therefore often present for weeks to months before the diagnosis of TB is confirmed or even considered. The physical examination may show abnormal chest auscultatory findings, hepatosplenomegaly, and/or lymphadenopathy. Although widespread lymphatic TB is frequent in AIDS patients, generalized lymphadenopathy occurs even more commonly with HIV-related lymphoid hyperplasia, and also occurs with Kapo-

si's sarcoma and B-cell lymphoma. The chances that lymphadenopathy represent mycobacterial or other specific disease (as opposed to nonspecific lymphoid hyperplasia) increase significantly when fever is present or when the lymph nodes are tender, fluctuant, matted, or disproportionately large and growing in a regional area (eg, the neck). In these settings we usually perform a lymph node biopsy. Hepatomegaly and abnormal liver function tests are also common among AIDS patients with TB but are also nonspecific findings. However, elevated alkaline phosphatase with a normal bilirubin does favor a diagnosis of granulomatous liver disease.

Extrapulmonary TB is particularly common among HIV-infected patients and, in the presence of a positive HIV-antibody test, it fulfills the revised (September 1987) Centers for Disease Control surveillance case definition for AIDS.[26] Lymphatic and disseminated TB (miliary TB and TB in two or more noncontiguous organs) are the most common extrapulmonary presentations; however, all other, often "unusual," forms of TB are also seen.[7-12,23,24] Tuberculous brain abscesses,[10,11,27,28] spinal cord abscesses,[29] meningomyelitis,[30] pericardial effusion,[31] pericardial cutaneous fistula,[32] retrogastric mass with a gastric ulcer,[33] mediastinal lymph-node esophageal fistula,[6] rectal abscess,[11] testicular abscess,[34] peritonitis with retroperitoneal lymphadenopathy (presenting as abdominal masses),[35] soft tissue abscesses,[11] generalized lymphadenopathy,[10,11,23] as well as positive blood and stool cultures[36,37] have all been described in patients with HIV infection.

The proportion of TB patients with HIV infection or AIDS who have extrapulmonary TB ranges from 32% to 76%; the proportion that has pulmonary TB ranges from 60% to 79%. (Pulmonary and extrapulmonary TB often coexist in HIV-immunosuppressed patients because of the tendency toward disseminated tuberculous disease.) By contrast, only 11% to 20% of TB patients without HIV infection or AIDS have extrapulmonary TB.[6,10,11,13,19,23]

When pulmonary TB is present, the radiographic picture is often atypical and may reveal lower lobe infiltrates or a diffuse bilateral miliary pattern.[11,13,23,38] Hilar and paratracheal lymphadenopathy are common (Fig 1), while cavitary disease is relatively uncommon.[19,38] Although

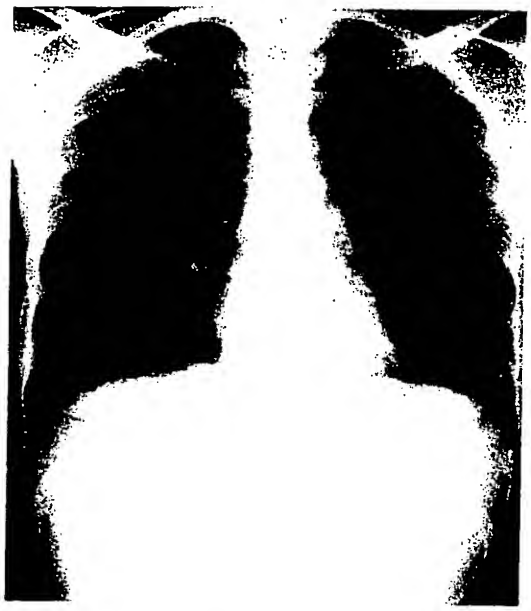

**Fig 1. Chest radiograph of a 28-year-old HIV seropositive IV drug abuser with a history of chills, fever, night sweats, and weight loss and no previous AIDS-related illnesses. The roentgenogram shows hilar adenopathy most prominent on the right and clear lung fields. Sputum smears and cultures were negative for mycobacteria, but culture of bronchoalveolar lavage fluid grew *M tuberculosis*.**

this chest radiographic pattern resembles primary TB, epidemiologic evidence suggests that most patients have reactivation TB with dissemination to regional (hilar) and distant lymph nodes because of the immune deficiency.[38] When pleural effusions occur, they tend to be small and, in disseminated TB, are often bilateral.[19,38] The chest radiograph may even appear normal despite the presence of disseminated TB and/or positive sputum cultures for *M tuberculosis*.[38] Finally, TB can coexist with other AIDS-related infections, and it is not uncommon to diagnose *P carinii* pneumonia (PCP) and pulmonary TB in a patient with bilateral pulmonary infiltrates suggestive of PCP alone (Fig 2). "Classical" tuberculous apical cavitary infiltrates and/or large unilateral pleural effusions can be seen in HIV-infected tuberculous patients but are relatively uncommon.[23,38]

## DIAGNOSIS

Because HIV-infected patients who develop TB often present with nonspecific symptomatology, atypical chest radiographic patterns, and

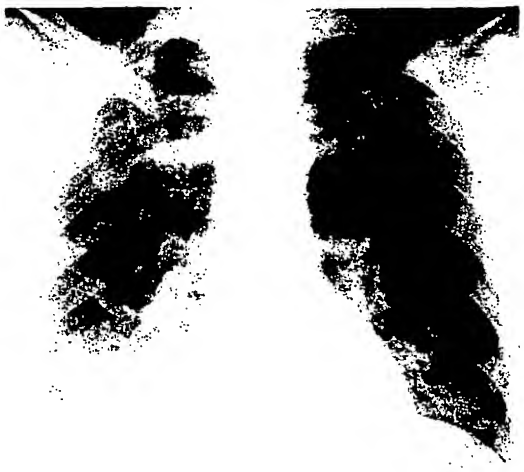

**Fig 2. Chest radiograph of a 36-year-old HIV seropositive homosexual male with fever and increasing shortness of breath. The chest radiograph shows a diffuse interstitial infiltrate. Initial sputum smears were negative for mycobacterial and other pathogens. Bronchoalveolar lavage fluid and transbronchial lung biopsy specimens showed *P carinii* pneumonia, which responded only partially to trimethaprim—sulfamethoxazole therapy. The initial sputum culture subsequently revealed *M tuberculosis*.**

extrapulmonary, disseminated or unusual disease, the physician must maintain a high index of suspicion for TB in this population. Among HIV-infected patients, this is particularly true for Haitians, IV drug abusers, other immigrant or indigenous groups in whom tuberculous infection is highly prevalent, those with a past history of a positive tuberculin skin test, or those with a history of recent TB exposure.[11,14]

The evaluation of a patient with suspected or proven HIV infection should include a careful history and physical examination, baseline chest roentgenogram and tuberculin skin test. If there are pulmonary symptoms or any other evidence for pulmonary disease, sputum smears and cultures for mycobacterial and other pathogens should be obtained. When necessary, sputum should be induced with aerosolized hypertonic saline solution. If there is objective evidence for pulmonary parenchymal disease (ie, abnormal chest roentgenogram, increased alveolar-arterial oxygen gradient, or abnormal gallium scan) and the sputum smear is nondiagnostic, a fiberoptic bronchoscopy with broncho-alveolar lavage and transbronchial lung biopsy should be performed. All specimens should be smeared and cultured for mycobacterial and other opportunistic pathogens, and tissue specimens should be examined for the presence of granulomas. *M tuberculosis* may be cultured from sputum, bronchoalveolar lavage fluid, or lung tissue, even though lung fields appear clear on the chest x-ray, granulomas are absent in lung tissue, acid-fast bacilli (AFB) cannot be demonstrated, and/or nontuberculous pulmonary infection is evident.[38] In HIV-immunosuppressed patients with pulmonary TB, gallium scans frequently show uptake in the mediastinal and hilar lymph nodes, which is not the case in PCP.[39] On rare occasions mediastinoscopy with biopsy is necessary for diagnosis.

If pulmonary disease is not present, and disseminated or extrapulmonary mycobacterial disease is suspected (eg, fever of unknown origin), an aggressive diagnostic approach should be undertaken to obtain mycobacterial smears and cultures from extrapulmonary body fluids and tissue sites. Mycobacterial smears and cultures should be obtained from urine, stool, and blood, and biopsies of bone marrow, lymph node, and liver may also be necessary. Samples and biopsies from other sites (ie, cerebrospinal, pleural, pericardial or peritoneal fluids, pleura, skin, subcutaneous tissue, pericardium, brain or intra-abdominal masses) may be necessary when pathology at these sites is clinically indicated. Computed Tomography scans of the head, chest, and abdomen, gallium scans, liver-spleen scans, abdominal sonograms, and echocardiograms may all be useful to detect tuberculous sites and to direct biopsies or aspirations of fluid.[27,28,31,33,35,40]

All specimens from patients with proven or suspected AIDS should be routinely smeared and cultured for AFB. The time for recovery and identification of mycobacteria from all specimens may be shortened with use of the Bactec radiometric system (Johnston Laboratories, Towson, MD). When used with an isolation-lysis-centrifugation system (Dupont Co, Wilmington, DE) and the sediment plated on a 7H11 agar, the isolation of mycobacteria from blood is enhanced and the degree of mycobacteremia can be measured.[37]

The tuberculin skin test is often negative (50% to 93%) in HIV-infected patients who present with TB. Nevertheless, a significant number of these patients (up to 50%) may still have a

positive tuberculin skin reaction, which may be useful in directing care.[10,11,13,19,23] For example, if an HIV-infected, tuberculin-reactive patient is symptomatic (eg, fever of unknown origin), and active TB cannot be excluded initially, full (multidrug) anti-TB therapy should be instituted. If TB is excluded subsequently, preventive therapy should consist of isoniazid (INH) for 12 months or, alternatively, INH plus rifampin (RIF) for a total of 6 months. If TB is subsequently diagnosed or considered likely, full anti-TB therapy is continued as discussed below.

## TREATMENT

Guidelines for treatment of TB in patients with AIDS or HIV infection have been published by the American Thoracic Society and Centers for Disease Control.[41,42] For adults, the recommended drugs and dosages are INH 300 mg/d, RIF 600 mg/d (or 450 mg for patients weighing less than 50 kgs), and pyrazinamide (PZA) 20 to 30 mg/kg/d. Pyrazinamide is administered during the first two months of therapy and then discontinued. Ethambutol, 25/mg/kg/d, should be included in the initial treatment regimen if INH resistance is suspected. Ethambutol may also be used for the first 2 months if PZA is not or cannot be added. Treatment with INH and RIF should continue for a minimum of 9 months of treatment and for at least 6 months after documented culture conversion as evidenced by three negative cultures. It is our practice to continue INH and RIF for a total of 12 months and for 9 months after culture conversion. Drug susceptibility tests should be performed routinely and the treatment regimen revised if there is resistance to the drugs being used. If either INH or RIF is not included in the treatment regimen, therapy should be continued for a minimum of 18 months and for at least 12 months after culture conversion. In this situation, appropriate therapy might consist of either INH or RIF, plus ethambutol for a minimum of 18 months, supplemented with PZA and streptomycin for the first 3 to 6 months. When noncompliance is anticipated or suspected, a fully supervised program with direct administration of therapy should be initiated.[41]

Anti-TB chemotherapy should be initiated promptly when AFB are found in specimens from an HIV-infected patient. Treatment should not be withheld on the presumption that the AFB might represent untreatable MAI or other nontuberculous mycobacteria. Like TB, MAI infection is common among patients with AIDS. In contrast to TB, the contribution of MAI infection to AIDS morbidity and mortality is unclear; there is no evidence that MAI is communicable from infected individuals to the general population and there is currently no effective chemotherapy for MAI that prolongs life or consistently ameliorates symptoms.[42] Therefore, when AFB are found in specimens from HIV-infected patients, initial therapy must be directed against the more virulent and contagious *M tuberculosis*. Treatment can later be changed, continued, or discontinued at the physician's discretion if the culture subsequently reveals nontuberculous mycobacteria.[42,43]

Most patients with TB and HIV infection respond well to therapy, and with few exceptions the drugs appear to be well tolerated. In a retrospective study of patients with TB and AIDS, Pitchenik et al found that positive mycobacterial sputum cultures converted to negative in all 10 evaluable patients within 1 to 4 months of treatment, which included INH and RIF. When followed an additional 2 to 18 months, there were no bacteriologic relapses. Although mild to moderate elevations in serum aspartate transaminase levels were seen in all patients, the drugs were well tolerated.[10] Chaisson et al, in a study of 12 patients with AIDS and pulmonary TB, found a higher incidence of adverse drug reactions (26%), which required change in therapy. However, all converted their positive sputum to negative within 3 to 10 months of starting anti-TB chemotherapy. One patient who was noncompliant with treatment relapsed after sputum conversion. A second patient with an INH-resistant organism developed central nervous system TB despite sputum conversion and continuation of appropriate anti-TB drugs.[13] In an ongoing prospective study conducted at the Dade County Public Health Department, 34 (96%) of 36 HIV-seropositive patients with pulmonary TB converted their smears and cultures to negative within 3 months of therapy and 13 (93%) of 14 HIV seropositive patients with extra pulmonary TB (primarily lymphatic) showed evidence of clinical response to chemotherapy within 3

months. In most patients, therapy consisted of INH and RIF alone, but PZA and/or EMB were added in some. Of 12 patients who completed their therapy and were followed-up for 4 months, two relapsed and were documented to be noncompliant with therapy. Despite mild elevations of serum aspartate transaminase in most patients, and adverse reactions such as itching or rash in some, only four patients (less than 10%) required changing or stopping the anti-TB chemotherapy.[19,23]

Anti-TB drug toxicity is often difficult to monitor because hematologic, hepatic, and dermatologic problems frequently occur from nontuberculous AIDS-related infections or their treatments, or may be a result of the mycobacterial disease itself.[11,19,23] Mild symptoms or minor laboratory abnormalities should not preclude the use of vital anti-TB drugs.[42]

Although TB in HIV-immunosuppressed patients usually responds to therapy, the appropriate duration of chemotherapy to prevent relapse once anti-TB drugs are stopped remains unknown. Further, HIV-infected patients with TB usually contract subsequent life threatening nontuberculous infections within 1 to 2 years.[10,11,13,24] Therefore, lifetime follow-up, including periodic mycobacteriologic examinations, is important in this population. Some experts suggest that HIV-infected patients with TB should have INH continued for life.[44]

Inherent in the concept of appropriate treatment and follow-up is the issue of knowing which patient who presents with TB should also be screened for HIV infection. Serologic testing for HIV and counseling should be performed in TB patients who are in risk groups for HIV infection, have manifested extrapulmonary or unusual TB, are diagnosed in an area where AIDS is prevalent, and/or are in an age group in which most HIV infections have been found . Knowing which patients with TB are seropositive for HIV is important for the following reasons: (1) The recommended treatment regimen differs from that for the general population.[41,42] A minimum of three initial anti-TB drugs (INH, RIF, and PZA) are suggested and INH and RIF are continued for a total of at least 9 months. Six month, short-course chemotherapy is not currently recommended. (2) Lifetime follow-up is necessary after completion of anti-TB therapy. (3) Physicians are alerted to the probability that other AIDS-related infections will soon follow. (4) Individuals can be identified who may benefit from anti-HIV agents (zidovudine) and other prophylactic regimens (ie, inhaled pentamidine to prevent PCP).[6] (5) Individuals can be counseled to prevent the spread of HIV infection to others.[45] (6) A positive HIV serology establishes the diagnosis of AIDS if the patient has extrapulmonary TB.[26] A diagnosis of AIDS may extend a patient's social service and disability benefits.

*Prevention*

All patients with documented HIV infection should receive a tuberculin skin test, unless there is a history of prior TB or a prior positive tuberculin skin test. If a significant skin reaction is found and active TB has been excluded with a chest roentgenogram and clinical evaluation, then INH preventive therapy should be administered for 12 months regardless of the patient's age.[42,46] A significant tuberculin skin reaction should be considered 5 mm or more of induration in an HIV-infected individual.[47] If the patient is anergic but has recently been started on zidovudine (AZT), it is reasonable to repeat the skin test in 2 months because immune restoration produced by the drug plus the tuberculin booster effect might restore a falsely negative skin test back to positive. Anergic, HIV-seropositive persons who have a radiographic abnormality consistent with old TB or a previously positive tuberculin skin test should also receive INH prophylaxis once active TB is excluded. In addition, because tuberculous infection is extremely high among Haitian immigrants,[14] an HIV-infected Haitian-born patient who is anergic may be treated with INH prophylaxis once active TB has been excluded. This principle may be applied to other immigrant or indigenous populations in whom the prevalence of tuberculous infection is known to be very high. Since IV drug abuse itself has been considered a risk factor for TB,[15] IV drug abusers with positive tuberculin skin reactions should receive for INH prophylaxis regardless of HIV status and regardless of age.[6,47] Persons in other risk groups for AIDS in whom the HIV status is negative or unknown should also receive a tuberculin skin test. If a significant reaction is

found, they should at least be managed according to the American Thoracic Society/Centers for Disease Control preventive therapy guidelines for the general population.[41]

Preventive therapy also includes appropriate management of active TB cases. Any HIV-infected patient with an undiagnosed pulmonary infiltrate should be placed on standard respiratory precautions until active TB has been ruled out.[48] Physician and health personnel directly involved in sputum induction, bronchoscopy, management of intubated patients and aerosol medication administration (eg, pentamidine) should take special precautions.[47-49] Local health departments should be notified and contact investigations carried out for patients with positive AFB smears (pending culture results) and/or positive cultures for *M tuberculosis*.[50] Close contacts who are HIV infected should receive INH preventive treatment (after active TB is excluded) regardless of age or tuberculin skin test status. BCG (and other live attenuated vaccines) should not be administered to HIV infected patients.[42]

TB is the only AIDS-related disease that can be transmitted via the aerosol route from an infected individual to the general population. As the millions of asymptomatic individuals who are currently HIV infected become increasingly immunosuppressed, and as the AIDS epidemic continues to grow, increasing numbers of tuberculous infected patients with AIDS will contract TB, and they, in turn, will transmit the infection to their contacts. A significant increase in the incidence of TB both in the United States and worldwide can therefore be projected unless preventive public health measures are instituted as previously discussed.[6,42,43,47,51,52,53] Fortunately, TB in the HIV-infected patient is readily treatable and probably preventable with conventional anti-TB drugs.

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